Remarks

Claims 1, 4-8, 11-18, 20, 24-31, and 33 are pending. Claims 1, 11, 13-15, 17, 18, and 24-29 have been amended. Claims 5, 7, 8, 13-15, and 24 have been withdrawn as being directed to a non-elected species. However, it is Applicants' understanding that once the elected species has been determined to be free of the prior art, the withdrawn claims will be examined on the merits.

Claim 1 has been amended to number each element of the claimed device and to correct grammatical errors, as suggested by the Examiner. Claim 1 was further amended to specify that the polymer is a bioerodible polymer. Support for this amendment can be found in the specification at least at page 5, lines 1-12. Claim 1 has also been amended to define a reinforcing feature of the polymer composition, as discussed in more detail below. Claims 13, 15 and 24 have been amended to depend from claim 1. Claim 14 was amended to correct a grammatical error. Claims 11, 17, 18, and 25-29 have been amended to correct antecedent basis.

The specification has been amended at page 1 to specify the relationship between the present application and a priority application and to provide updated status information for a priority application. No new matter has been added by these amendments.

Rejection Under 35 U.S.C. § 103

Claims 1, 3, 6, 11, 12, 16, 25, 30, and 33 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 4,961,740 to Ray *et al.* ("Ray"), in view of U.S. Patent No. 5,741,329 to Agrawal *et al.* ("Agrawal"). Claim 3 was previously canceled. Thus it appears that the rejection is directed at claims 1, 6, 11, 12, 16, 25, 30, and 33. Claim 4 was rejected under 35

U.S.C. § 103(a) as obvious over Ray in view of Agrawal, and in further view of U.S. Patent No. 5,192,327 to Brantigan ("Brantigan"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The examiner has indicated that claims 17, 18, 20; 26-29 and 31 were objected to but allowable over the prior art based on the incorporation of a reinforcement feature such as reinforcing fibers or crosslinking. Accordingly, claim 1 was amended to require the composition to include one or more features that are used to strengthen the composition, which is particularly important in orthopedic applications. The claim now specifies a strengthening material selected from the group consisting of crosslinked monomers , reinforcing fibers, self-reinforcing aligned fibers of the polymer, degradable polymeric scaffolds, and interpenetrating networks. (see page 9, lines 17-20; page 19, lines 20-29, page 20, lines 25-28, page 22, lines 21-31; page 22, line 32-page 23, line 8).

As demonstrated by the copy of the enclosed article, "Biomechanical Analysis of Biodegradable Interbody Fusion Cages Augmented with Poly(Propylene Glycol-co-fumaric acid)" by Kandziora, *et al.*, augmentation of a PLGA device with polypropylene glycol-co-fumaric acid increases the strength of the PLGA so that it is similar to titanium.

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988).

Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is ***rigorous*** application of the requirement for showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999) (emphasis added). The references must themselves lead those of ordinary skill in the art to what is claimed, otherwise the claims are not obvious.

Ray

Ray describes an interbody fusion cage formed of stainless steel, titanium, ceramics, or a super-strength polymer or composites, such as super-high-density polyethylene, glass, or graphite (col. 4, lines 31-35). Ray states that polymer can be biodegradable (col. 4, line 39), but does not disclose any biodegradable polymers nor the inclusion of a pH-neutralizing agent or a buffering agent. Ray emphasizes the importance of maintaining the cage's structural strength (see e.g. col. 4, lines 3-14 and lines 30-35). The fusion cage has a threaded outer surface and an internal cavity which is adapted to be filled with bone chips (col. 3, lines 39-41). Ray does not describe using up to 75% of a pH-neutralizing agent or buffering agent to form the interbody fusion cage, though it states that hydroxyapatite can be used as a bone activating matter placed in

the cavity of the cage (col. 4, lines 46-48). Ray does not suggest using a reinforcing material with a biodegradable polymer, as defined by the amended claims.

Agrawal

Agrawal describes an implantable, biodegradable device formed of a biodegradable porous polymer and a pH-controlling substance or buffering agent (col. 2, lines 6-42; col. 8, lines 17-28; abstract). The biodegradable polymer can be polyglycolic acid, polylactic acid, and poly(glycolic acid-co-lactic acid) (col. 3, lines 50-59). The pH buffering agent or pH-controlling agent can be calcium carbonate, sodium bicarbonate, calcium hydroxyapatite, or a mixture thereof (col. 4, lines 23-26). The implantable device may be in the form of a pin, screw, staple, nail, suture, or fiber (col. 4, lines 53-60). Agrawal notes that the device may be suitable for long-term implantation and in such cases degrades over a period range from 1 week to 2 years (col. 5, lines 14-17). Agrawal also does not suggest using one of the claimed reinforcing materials in combination with the implantable device.

Combination of Ray with Agrawal

There is no disclosure or suggestion in either of the references to combine Ray with Agrawal to yield a reinforced device as claimed. Ray teaches away from such a device through the selection of materials such as titanium and ceramics. Agrawal is focused on degradation occurring over a relatively short period of time. Ray focuses on metal and ceramic materials for the formation of the cage, stating that stainless steel is the preferred embodiment (col. 4, lines 30-45). To the extent that he even mentions polymers, he stresses the need for *super-strength*

polymer characteristics, as found in polyethylene, glass, or graphite, none of which are biodegradable. Agrawal describes degradable implantable devices made from *porous, biodegradable* polymers such as PLA, PLGA, and copolymers thereof. Agrawal does not disclose nor suggest the inclusion of any materials that would produce material with sufficient strength for use in an interbody spinal fusion device.

However, even if one of ordinary skill in the art combined Ray's disclosure of a fusion cage with a large internal cavity with Agrawal's disclosure of biodegradable polymers with pH buffering agents, he would not produce the claimed devices. The implantable device as described by Agrawal at col. 4, lines 1-34, is formed of a polymer in combination with sodium bicarbonate as an alkaline agent of choice in an amount of 1% to 99% by weight or 5% to 50% by volume of the polymer used. Sodium bicarbonate is highly water soluble and has no mechanical strength when placed in water. Thus, if a fusion cage with a *large internal cavity* is constructed from such a material, it would degrade quickly and not provide the structural support required to function as a fusion cage.

Applicants have described a means for producing a viable resorbable interbody spinal fusion device comprising a biodegradable polymer including means for reinforcement, a neutralizing agent, and one or more void spaces that contain a bony graft material which has a mechanical strength suitable to withstand the great strain placed on spinal implants. As the examiner has acknowledged, features such as reinforcing fibers and polymer crosslinking are not

even mentioned by either Agrawal nor Ray. For these reasons, Ray in combination with Agrawal cannot make obvious claims 1, 6, 11, 12, 16, 25, 30, and 33.

Brantigan

Brantigan describes a prosthetic device to integrate with and support vertebrae in a vertebral column (col. 1, line 64 to col. 2, line 43). The prosthetic device has to be biologically acceptable but inert (col. 1, lines 64-65). One of ordinary skill in the art would recognize that the term "inert" refers to being chemically stable, *e.g.*, the device would not degrade under physiological conditions when used in a human body. This definition is confirmed by the description at col. 2, lines 52-55 which states that the device provides "a permanent mechanically secure repair with living tissue." Thus Brantigan does not disclose a bioerodible device.

Combination of Ray and Agrawal in further view of Brantigan

There is no disclosure or suggestion in the references to combine Ray with Agrawal or to combine both of these references with Brantigan. Agrawal describes implantable devices formed from porous, biodegradable polymers, while both Ray and Brantigan disclose non-degradable, non-porous devices. Thus, at most one of ordinary skill in the art could be motivated to combine only Ray with Brantigan. However, if Ray was combined with Brantigan, the claimed device would not be obvious to one of ordinary skill in the art. Neither Ray nor Brantigan describe a pH buffering or neutralizing agent as required in the claimed device. Nor do they provide the motivation for one of ordinary skill in the art to modify their devices to form a device having up

to 75% a pH buffering or neutralizing agent, as defined by the claims. None suggest the use of reinforcing means.

Even if one of ordinary skill in the art combined Ray with Agrawal and with Brantigan, the claimed devices would not be obvious. As noted above, the combination of Ray with Agrawal would produce devices that lack the necessary strength to serve as an interbody spinal fusion device. The addition of Brantigan does not does not cure the deficiencies of Ray and Agrawal. Brantigan discloses a biologically inert prosthetic device that contains bone graft material in the open central portion of the device (col. 1, lines 64-65 and col. 2, lines 14-17). Brantigan does not disclose a bioerodible polymeric material which is suitable for the formation of an interbody spinal fusion device. Therefore the combination of Ray with Agrawal and Brantigan would not make claim 4 obvious.

Claim Objections

Claims 1 and 17 were objected to due to grammatical errors. In response, claims 1 and 17 have been amended, as suggested by the Examiner.

Claims 17, 18, 20, 26-29, and 31 were objected to as being depended upon a rejected base claim. Applicants respectfully traverse this objection in view of the amendments to claim 1. As noted above, claim 1 is non-obvious in view of the cited art. Therefore, dependent claims 17, 18, 20, 26- 29, and 31, should be allowable.

Allowance of claims 1, 4-8, 11-18, 20, 24-31, and 33, as amended, is respectfully solicited.

Respectfully submitted,

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Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, July 22, 2004, to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.

Rivka D. Monheit

Date: July 22, 2004

BIOMECHANICAL ANALYSIS OF BIODEGRADABLE INTERBODY FUSION CAGES AUGMENTED WITH POLY(PROPYLENE GLYCOL-CO-FUMARIC ACID)

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ABSTRACT

Study Design: Three different types of biodegradable poly(L-lactide-co-D,L-lactide; PDLLA) cages with and without augmentation of a biodegradable poly(propylene glycol-co-fumaric acid) scaffold were compared to autograft and metallic cages of the same design and size by determining the stiffness and failure load of the L4/5 motion segment of cadaveric human spines.

Objectives: To determine how these devices limit the range of motion in the lumar spine compared to a metallic cage. If biomechanically equivalent, biodegradable spinal fusion systems ultimately could reduce local stress shielding and diminish the incidence of clinical complications including device-related osteopenia, implant loosening and breakage.

Summary of Background Data: Previous studies in dogs and humans have demonstrated vertebral body osteopenia as a result of instrumented spine fusions. To the authors knowledge, neither an *in vitro,* nor an *in vivo* biomechanical analysis of a biodegradable interbody fusion system has been performed.

Methods: Forty-eight L4/5 motion segments were isolated from 22 male and 26 female human donors with an average age of 49.6 +/-2.7 (36 - 55) years. Cages of similar dimensions and design including a threaded, hollow, porous titanium BAK cage and three different BIO-cages (BIO-cage 1 – pure polymer, BIO-cage 2 - polymer plus hydroxyapatite buffer, BIO-cage 3 – polymer plus nano-sized hydroxyapatite) produced from the same (poly(L-lactide-co-D,L-lactide) polymer were tested in a comparative analysis to intact motion segment, interbody implantation of autograft, and a BIO-cage augmentated with an expandable biodegradable foam-scaffold fashioned from poly(propylene glycol-co-fumaric acid).

Results: All cages were able to increase stiffness and failure load of the unstable motion segment significantly ($p < 0.01$). In comparison with the bone graft, the BAK-cage ($p < 0.01$), BIO-cage 1 and 3 ($p < 0.05$) were able to increase stiffness and failure load. There was no significant difference between BIO-cage 2 and the bone graft. Augmentation of Bio-cage 1 with the foaming PPF-scaffold resulted in higher stiffness and similar failure load as seen with the BAK cage.

Conclusions: By comparison, the *in vitro* lumbar spinal motion segment stiffness and failure load produced by implantation of a biodegradable interbody fusion cage augmented with an expandable PPF-scaffold is similar to that of the titanium BAK cage. This suggests that biodegradable anterior interbody fusion systems could be further developed for clinical applications.

Keywords: interbody fusion, biodegradable implant system, biomechanical analysis

PRECIS:

Biodegradable poly(L-lactide-co-D,L-lactide) cages with and without augmentation of a biodegradable poly(propylene glycol-co-fumaric acid) scaffold were compared to autograft and metallic cages by determining the stiffness and failure load of the L4/5 motion segment of cadaveric human spines. The spinal motion segment stiffness and failure load produced by implantation of a biodegradable interbody fusion cage augmented with an expandable PPF-scaffold is similar to that of the titanium BAK cage warranting further developed for clinical applications.

INTRODUCTION

Spine fusion remains the standard treatment for patients with spinal deformity, trauma, or segmental instability. However, some aspects of fusion surgery have been the focus of controversy. Its short-term risks include neural injury, wound problems, pseudarthrosis, and implant failure in cases where instrumentation is used. [19,21,29] Long-term effects of spine fusion remain incompletely documented; one area of particular concern is the risk of disuse osteopenia in the vertebral bodies at the level of the fusion. [17]

Stress-shielding has been seen in dogs who have undergone spine fusions. [3,4,5,11,16,21] Three of these studies, in which dual-photon absorptiometry (DPA) in the anteroposterior orientation was used, showed a decrease in the bone mineral density (BMD) of vertebrae that were bridged by rigid instrumentation. [3,4,23] Another study found histologic osteopenia but no significant BMD difference between fused and unfused spines by using DPA in the lateral position. [5] This apparent insensitivity of lateral DPA was attributed to the large transverse processes and the fusion mass, which, in dogs, lie lateral to the vertebral body and overlie the vertebral body on lateral scanning.[5] The presence of osteopenia indicated by anteroposterior DPA studies, however, was confirmed by additional histologic studies that showed device-related osteopenia. [3,4,21]

These studies by McAfee et al, [9] Shirado et al, [23] and Zdeblick et al.[28,29] did not only demonstrate that posterior instrumentation augmenting a posterolateral fusion produced a higher fusion rate than the non-instrumented spine, but also showed that higher rigidity of the instrumentation resulted in increasing fusion rates and the amount of "device-related osteoporosis". Biomechanically, the addition of spinal instrumentation led to significantly more stability. Thus, the stiffer constructs, which stress shielded the vertebrae, the higher the

rate of fusion. A biomechanically stronger fusion mass was found despite the "device-related osteoporosis."

Extrapolating results from these canine studies to human patients should be done with caution because of anatomic differences between canines and humans. The biomechanics of the spine of the bipedal human are quite different from those of the spine of the canine. [7,22] Pseudarthroses, for example, are much more common in humans than in animal spine fusion models. [22] Hence, device-related problems in the human spine remain poorly documented and long-term effects of the rigid spinal instrumentation may, in fact, be detrimental. One potential solution to the problem could be the use of a biodegradable spinal instrumentation system that, once fusion is achieved, would simply degrade over time thereby avoiding the stress-shielding and its associated clinical complications.

Poly-L-lactides and Polyglycolides and their copolymers have extensively been used for the manufacturing of orthopaedic implants. Since fast degradation appears to be associated with an increased rate of inflammatory foreign-body reactions, poly-L-lactide of long- and poly-L/D-lactide and poly-L/DL-lactide of intermediate duration have recently been introduced. In the absence of foreign-body reactions of clinical significance to poly-L-lactide implants, their biocompatibility has generally been described as favorable. [24,25] To decrease the possibility of an inflammatory responses even further and to enhance the overall osteointegration process of a biodegradable spinal implant, we incorporated a long acting hydroxyapatite buffer into a poly-DL-lactide (PDLLA) interbody fusion device. Furthermore, the used of nano- over micron-sized hydroxyapatite, and augmentation of a cage with an expandable biodegradable foam was expected to improve upon the mechanical characteristics of a fused segment. For these reasons, we tested PDLLA cages with and

without augmentation of a biodegradable poly(propylene glycol-co-fumaric acid) scaffold and compared them to autograft and a metallic cage of the same design and size by determining the stiffness and failure load of the L4/5 motion segment of cadaveric human spines. The human spine specimens were tested in flexion, extension, left and right lateral bending as well as left and right axial rotation.

MATERIALS AND METHOD

Specimens

Forty-eight intact adult cadaveric lumbar spine (L3 - S1) specimens. In addition, autologus iliac bone grafts was harvested from each donor. En bloc specimens were stored at -20° C until they were thawed in a water bath at 25° C prior to biomechanical testing. The L4/5 motion segment was isolated and the paraspinal muscles were removed. During the dissection, care was taken to preserve all spinal ligaments. The average age of the 22 male and 26 female donors was 49.6 +/-2.7 (36 - 55) years. Donor exclusion criteria included history of trauma, malignancy or metabolic disease. In addition each specimen was radiographed to confirm the absence of lytic lesions, fractures or any other bony abnormalities. In analogy to the surgical procedure employed in clinical practice, a complete L4/5 discectomy with resection of the anterior and posterior longitudinal ligament was performed. The endplates were decorticated using a high-speed diamond burr.

Cages

For comparative biomechanical analysis, cylindrical cages of similar design and dimensions were employed. The respective diameter was 15 mm and the length was 24 mm.

Metallic, threaded, hollow, porous titanium cages (BAK) were obtained from Spine Tech, Inc. (Minneapolis, MN, USA). All biodegradable cages shown in figure 1 (BIO-cage 1 to 3) were manufactured by Cambridge Scientific, Inc. (Boston, MA, USA) from the same polymer (poly(L-lactide-co-D,L-lactide), Resomer LR 708. The raw polymer was supplied by Boehringer-Ingelheim (Mannheim, Germany). BIO-cage 1 consisted of pure polymer. BIO-cage 2 consisted of polymer plus 10 micron size (20%w/w) hydroxyapatite buffer. BIO-cage 3 consisted of polymer (75%w/w) plus hydroxyapatite 10 micron size (20%w/w) plus nano-sized hydroxyapatite (5%w/w). All cages, including the BIO-cages were implanted according to producers information using the instrumentation and equipment of the BAK-cage (Spine Tech, Minneapolis, MN, USA). Specimens were kept moist during the tests.

Materials and Formulations

The general formulation of the biodegradable poly(propylene glycol-co-fumaric acid) scaffold used for the augmentation of the Bio-cages is shown in Table 1. PPF (Mw~5,000 by GPC) was synthesized from equimolar fumaric acid and propylene glycol in the presence of p-toluene sulfonic acid. [6,7] 1-Vinyl-2-pyrollidinone (VP), Benzoyl peroxide (BP), hydroquinone (HQ), and N-N-dimethyl-p-toluidine (DMPT) were purchased from Aldrich (USA) and used as received. Sodium bicarbonate (SB), and citric acid (CA) were purchased from Fisher Scientific (USA)

The liquid component (part II) consisting of VP, accelerator DMPT, and distilled water was added to the dry powdered mixture (part I) consisting of PPF, HA, SB, BP initiator, and CA to form a viscous putty-like paste resulting in a crosslinked polymer. The accelerator, DMPT, at a concentration of 0.03% w/w,

gave a working time of about 90 seconds. The stoichiometry requires a 1:3 mole ratio of CA:SB with a CA:SB weight ratio of 1.00:1.31.[2]

The reaction of CA/SB with water produces carbon dioxide, the blowing agent responsible for foam formation and expansion. Typically, this would result in formation a PPF foam with pore sizes of 100-300 microns (Figure 2). The stoichiometry requires a 1:3 mole ratio of CA:SB with a CA:SB weight ratio of 1.00:1.31. The moles of CO_2, which can be generated per gram of material, depend on the loading of CA/SB in the foaming cement. A 0.15% CA/SB loading would produce a 25% expansion at 37°C and 1 atm based on the above stoichiometry. In addition to the blowing agent, PPF formulation was crosslinked using vinyl pyrollidinone in the presence of an osteoconductive HA filler using techniques described previously. [10]

The hydroxyapatites used for the manufacturing of the biodegradable cages were: nano HA (group 1, median particle size = 40 nanometers, (as produced and characterized by Professor Ying at MIT [30-32]) and 10 μm HA sintered, spherical micron-HA (group 2, median particle size = 26 microns, commercially available from CAM Implants, The Netherlands). All HA preparations used in this study have been characterized using X-ray diffraction (XRD) to investigate the crystalline purity and size, photoacoustic Fourier transform infrared (PA-FTIR) spectroscopy to substantiate the molecular structure, and transmission electron microscopy (TEM) to determine the particle size and porosity.

Study protocol

Each spine specimen served as its own control and was tested in the following sequence: (1) intact (control group; n = 48), (2) after L4/5 discectomy and dissection of the anterior and posterior longitudinal ligaments (unstable group, n = 48). Finally, all spines were randomly assigned to one of the remaining study groups. (3) tricortical autologous iliac crest bone graft (n

= 8), (4) BAK-cage, (5) BIO-cage 1 (n = 8), (6) BIO-cage 2 (n = 8), (7) BIO-cage 3 (n = 8), and (8) Bio-cage 1 plus approximately 3.5 gram of the PPF/VP mix which was injected to the spinal segment to foam around the cage.

Stiffness Tests

The L4/5 motion segment was tested by a non-destructive flexibility method using a non-constrained testing apparatus described in detail elsewhere. [14] Pure bending moments were applied using a system of cables and pulleys to induce flexion, extension, left and right lateral bending and left and right axial rotation. Tension was applied to the cables with a material testing machine (Zwick 1456, Zwick GmbH, Ulm, Germany). Applied forces were measured with an axial load cell (Z 12, HBM, Darmstadt, Germany) mounted on the testing frame. Moments were calculated by multiplying the applied force by the radius of the pulley on the spine-testing fixture (Figure 3).

Three-dimensional displacements of the L4/5 motion segment were measured using sterophotogrammetric techniques (Qualysis, Inc., Sävebalden, Sweden). Two triangular non-linear diodes (Qualysis, Inc., Sävebalden, Sweden) were attached to the center of the spinous process of L4 and L5. The marker positions were detected with two cameras and recorded with a computerized motion analysis system (PC-Reflex, Qualysis Inc., Sävebalden, Sweden). The angular displacement of L4 in relation to L5 was calculated from marker position using custom-made computer software. The experimental error associated with this method was ± 0.12 degrees.

For testing, L3 was mounted in a rigidly fixed pot using PMMA (Technovit 3040; Heraeus Kulzer GmbH, Wehrheim/Ts, Germany) and S 1 was rigidly attached to the traverse bar

at the basis of the apparatus. This test setup resulted in a compressive preload of 6.8 N due to the weight of the fixation pot. Specimens were preconditioned with three cycles of 7.5 Nm load with a velocity of 1 mm/sec of the traverse bar before recording data.

Moments were applied in a quasistatic manner in increments of 0.5 Nm to a maximum of 7.5 Nm. Test modes were flexion, extension, left and right axial rotation, and left and right lateral bending. At each step the specimen was allowed to creep for 60 seconds to minimize viscoelastic response before data were recorded. Total range of motion (ROM) and angular displacement were measured in degrees. The mean apparent stiffness values were calculated from the corresponding load-displacement curves. The neutral and the elastic zone were determined.

Axial Compression Tests

After stiffness testing, specimens were tested in compression with the same uniaxial servohydraulic testing machine (Zwick 1456, Zwick GmbH, Ulm, Germany). Applied forces were measured with an axial load cell (Z 12, HBM, Darmstadt, Germany) mounted on the testing frame. For this test, the L4 and L5 vertebral bodies were mounted in pots using PMMA (Technovit 3040; Heraeus Kulzer GmbH, Wehrheim/Ts, Germany) and constrained from rotation during the test. Three triangular non-linear diodes (Qualysis, Inc., Sävebalden, Sweden) were attached to the pots and also to the interbody implants. The marker positions were detected with two cameras and recorded with a computerized motion analysis system (PC-Reflex, Qualysis, Inc., Sävebalden, Sweden). The axial displacement of L4 in relation to L5 and the displacement of the implant was calculated from marker position using custom-made computer software. The experimental error associated with this method was +/- 0.10 mm.

Axial compression displacement was applied to the specimen at a rate of 1mm/sec. Specimens were preconditioned with three cycles of 600 N load with a velocity of 1 mm/sec before data were recorded. At each step the specimen was allowed to creep for 60 seconds to minimize viscoelastic response. Finally, the compression test was continued until failure as evidenced by a drop in the real-time compressive load displacement curve. For both stiffness and axial compression testing, stiffness and failure load were calculated from the load displacement curves.

Statistical analysis

Comparison of ROM, neutral and elastic zone, stiffness and failure load for the different fixation techniques was performed using one way analysis of variance (ANOVA) and Fishers least significant difference (LSD) for post-hoc analysis. Statistical significant differences were defined at a 95% confidence level. The values are given as mean +/- standard deviation. SPSS (release 7.0, SPSS Inc. Chicago, IL.) software supported statistical evaluation.

RESULTS

Range of Motion and Stiffness Testing

In comparison to the unstable L4/5 motion segment, the BAK-cage and all Bio-cages similarly stabilized the L4/5 motion segment above the level intact motion segment with comparable limitation of ROM in flexion/extension, left and right lateral bending, and to rotation with statistically significant difference ($p < 0.01$). However, there was no statistically significant difference between the four cages. The respective data is shown in Figure 3 and 4 by normalizing the ROM-data to the intact L4/5 motion segment. Only the augmentation of the

Bio-cage 1 with the expandable, foaming PPF scaffold resulted in more restriction of ROM in the L4/5 motion segment with statistical significance on ANOVA testing. Furthermore, all cages showed a significantly higher flexional/extensional and bending stiffness when compared to the intact motion segment ($p<0.05$). However, no one single cage was any better or worse than one of the other. When used without the expandable foaming PPF scaffold, there was also no significant difference in rotational stiffness between the cages and the intact motion segment. However, the L4/5 motion segment was significantly stiffer than the intact motion segment upon rotational stresses when Biocage 1 was implanted in conjunction with the PPF scaffold. Moreover, there was no significant difference in ROM and stiffness between the different cages compared to the autologous bone graft.

Axial Compression Testing

In comparison with the intact motion segment, the stiffness and failure load was significantly higher than in the intact motion segment when a BAK cage was implanted ($p < 0.05$). As shown in figure 5, all L4/5 motion segments, in which any of the three BIO-cages (Bio-Cage 1 to 3) was implanted, were less stiff than the intact motion segment ($p < 0.05$). There was no significant difference between failure load of the intact motion segment and Bio-cage 1. However, failure loads in BIO-cage 2 and 3 were significantly lower than in the intact motion segment ($p<0.05$). The failure load in the L4/5 motion segment stabilized with Bio-Cage 1 that was augmented with the PPF scaffold was not only significantly higher than in the intact motion segment, but also higher than in the motion segments where a metallic BAK cage was implanted. There was no significant difference in stiffness upon axial loading between BIO-cage 2 and the bone graft.

Failure Mode

While failure of the bone graft always resulted from compression of the graft, motion segments, in which a BAK cage was implanted, failed by a split fracture of the vertebral body in five instances and by subsidence of the cages in another 3 specimens. All BIO-cages 1 failed by viscoelastic deformation. BIO-cages 2 and 3 collapsed and fractured (Figure 6).

DISCUSSION

Rigid spinal stabilization techniques with transpedicular screw instrumentation have resulted in increased fusion rates with better clinical outcomes compared with those without internal fixation.[5] On the other hand, rigid spinal implants may produce stress shielding and subsequent vertebral osteopenia. [1,4,6,12,16] Osteopenia in the vertebrae is of clinical importance because it eventually may lead to screw loosening and instrumentation failures. [4] McAfee et al [8,10] have reported this phenomenon using canine models in 1989. They concluded that increased biomechanical rigidity of the spinal construct was more favorable, resulting in a successful arthrodesis with an increased cross-sectional area of the posterolateral fusion mass despite the secondary vertebral osteoporosis. Dalenberg et al [4] reported the relationship between the incidence of screw loosening and device-related vertebral osteopenia induced by pedicle screw instrumentation using canine models in 1993. To date, no method has been effective in preventing vertebral bone mineral loss observed with stiff spinal implants. [5] This has motivated that author's present investigation of a biodegradable anterior spinal instrumentation system.

The intention of the current study was to quantify the stiffness and failure load of the L4/5 motion segment of cadaveric human spines, which were fused *in vitro* with different types of PDLLA cage with and without augmentation of a biodegradable poly(propylene glycol-co-

fumaric acid) scaffold. Tricortical autograft from the same donor and a metallic BAK cage of the same design and size served as controls. The cadaveric human spinal specimens were tested in flexion, extension, left and right lateral bending as well as left and right axial rotation. All stiffness and axial compression measurements were taken at the L4/5 level primarily for clarity of data presentation, and consistency in the experimental design.

Poly(L-lactide-co-D,L-lactide) was chosen on the basis of its superior mechanical strength and longer degradation times. Ultimately, this would pertain to future clinical applications. The choice of polymer and the additional use of nano-hydroxyapatite was based on the expectation that inflammatory responses frequently seen with faster degrading polyglycolides could be diminished or even avoided. In addition, nano-hydroxyapatite was chosen as part of the formulation for Bio-Cage 3 because of its potential to eliminate some of the disadvantages associated with the use of conventional hydroxyapatite. Nano-hydroxyapatite is more homogeneous and of higher purity and better mechanical properties of copolymer composites have been demonstrated when nano-apatite particles were used. Liu et al hydrothermally synthesized acicular nano-apatite (Nap) which was used as filler to make composites with a polyethylene glycol/poly(butylene terephthalate) (PEG/PBT) block copolymer (Polylactide 70:30). [13] The mechanical properties and the physiochemical characteristics of the composites, such as Young's modulus, swelling degree in water and the calcification behaviour, were determined. Nap had a strong ability to promote the calcification of composites when incorporated into Polylactide 70:30. Nap had a prominent stiffening effect for Polylactide 70:30.

An additional stiffening effect of the L4/5 spinal motion segment was expected with the use of the expandable, biodegradable poly(propylene glycol-co-fumaric acid) scaffold, which practically acted as a cement. During polymerization of the formulation, the reaction of citric

acid (CA) and sodium bicarbonate (SB) causes the formation of carbon dioxide, which is responsible for foam formation and a 25% expansion at 37°C and 1 atm. Expansile pressures of approximately 50 Psi have been noted. [10] Thus, the PPF foam was likely to fill the intervertebral disc space entirely with intimate contact into all bony crevices of both adjacent endplates. This void filling effect has been demonstrated in other studies utilizing this material. [10] Therefore, the PPF was used to essentially cement the interbody fusion implant (Bio-Cage 1) into place, thus, further stiffening the fused spinal motion segment.

BAK-Cages have been tested *in vitro* biomechanically on human lumbar spines. [18,20] Nibu [18] and Rapoff [20] demonstrated significant reduction of lumbar spinal segment motion after implantation of a BAK-Cages. In addition, the rigidity of the tested lumbar spinal motion segments was higher when compared to similar segments that were left intact. Results of this *in vitro* comparative mechanical analysis of this study appeared to support the use of a biodegradable anterior interbody spinal fusion system by reproducing results of these earlier studies at least in part. While motion segments immobilized with any of the three Bio-cages were less stiff to flexion/extension, left and right lateral bending, as well as axial rotation than motion segments immobilized with the BAK cage, additional use of the foaming PPF scaffold to augment the spondylodesis with Bio-cage 1 resulted in a significant increase in the stiffness of the fused L4/5 motion segment. In fact, motion segments immobilized with Bio-cage 1 and the PPF scaffold showed the highest stiffness and highest failure loads of all types of interbody implants used. In axial compression, stiffness and failure load was significantly higher than in the intact motion segment with the BAK cage. Furthermore, all Bio-cages were less stiff than the intact motion segment when tested in axial compression. Most importantly, the failure load in the L4/5 motion segments stabilized with Bio-Cage 1 and additional augmentation with the

PPF scaffold was not only significantly higher than in the intact motion segment, but also higher than in the motion segments where a metallic BAK cage was implanted.

The failure load observed with the metallic BAK cage averaged 7.42 kN. The physiologic intradiscal peak pressure has been studied by Nachemson. [17] Depending on the body position it may vary between two to three times the body weight. Intradiscal *in vivo* strain measurements in the L4/5 lumbar spinal motion segment of primates showed that the highest measurable strain values were indicative of loads in excess of 2.8 times body weight for the 40-kg animals. [9] In humans, intradiscal pressures have been measured in one subject. [27] These measurements indicated that the intradiscal pressure depends on the kind of preceding activity, posture, external loads and muscle activity. Pressure values observed were as follows: relaxed standing 0.5 MPa; standing flexed forward 1.1 MPa; standing extended backward 0.6 MPa; sitting unsupported 0.46 MPa; maximum values during lateral bending 0.6 MPa, during axial rotation 0.7 MPa, lifting a 20 kg weight with a round flexed back 2.3 MPa, with flexed knees 1.7 MPa, close to the body 1.1 MPa; sitting unsupported relaxed 0.45 MPa, actively straightening the back 0.55 MPa, with flexion 0.9 MPa; non-chalant sitting 0.3 MPa. When using this data set to verify a biomechanical model adjusted to the individual characteristics by a comparison of measured and predicted intradiscal pressures, the L 4/5 motion segment of a patient weighing 80 kg should experience peak loads on the order of 2.24 kN. Hence, the failure loads of all Bio-Cages (Bio-Cage 1: 5.89 kN; Bio-Cage 2: 3.22 kN; Bio-Cage 3: 4.74 kN) were above the level of physiological loads.

This *in vitro* study clearly demonstrated the feasibility of utilizing a biodegradable interbody spinal fusion cage in the human spine. From a mechanical perspective, these devices, at least if made from the pure polymer, i.e. Bio-cage 1, appear equally capable of immobilizing

a spinal fusion segment as if with a metallic BAK cage. The lower axial failure loads observed with Bio-cage 2 and 3 appear related to inhomogeneous mixing of the various hydroxyapatite inclusions. On the presumption of enhanced biocompatibility and accelerated tissue regeneration, these materials will have to be further materially improved to demonstrate mechanical properties that are at least equivalent to the pure polymer prior to considering them further for clinical implant materials. Most remarkably, however, is the ability of the injectable, expandable, foaming PPF-scaffold to increase the stiffness and failure load in the fused L4/5 human motion segment significantly approximately by 40% to 50%. If these effects could be replicated for selected anterior and posterior clinical spinal fusion applications, such a material could prove eminently worthwhile for the development of biodegradable implants for spinal fusion and repair ranging from bone graft substitutes or extenders, to injectable void fillers for even minimal invasive techniques and procedures. While acting as a cement and an void filler, the foaming PPF-scaffold could effectively contribute to the stress dispersion within a spinal motion segment immobilized with a cage whose modulus of elasticity is higher than and, thus, potentially diminish the occurrence of complications seen with anterior spacer devices, which commonly fail by intrusion into the endplate or collapse. For these reasons, we propose further development of a biodegradable anterior interbody fusion systems for clinical applications.

ACKNOWLEDGEMENTS

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LITERATURE

1. Akeson WH, Woo SL, Rutherford L, Coutts RD, Gonzalves M, Amiel D. The effects of rigidity of internal fixation plates on long bone remodeling: A biomechanical and quantitative histological study. Acta Orthop Scand 1976;47:241-9.

2. Bondre SP, Lewandrowski KU, Cattaneo MV, Hasirci V, Gresser JD, Wise DL, Tomford WW, Trantolo DJ. Biodegradable foam coating of cortical allografts for improved osteoconduction. Tissue Engineering, 2000; 6(3): 217–227.

3. Craven TG, Carson WL, Asher MA, Robinson RG. The effects of implant stiffness on the bypassed bone mineral density and facet fusion stiffness of the canine spine. Spine 1994;19:1664-73.

4. Dalenberg DD, Asher MA, Robinson RG, Jayaraman G. The effect of a stiff spinal implant and its loosening on bone mineral content in canines. Spine 1993;18:186-66.

5. Farey ID, McAfee PC, Gurr KR, Randolph MA. Quantitative histologic study of the influence of spinal instrumentation on lumbar fusions: A canine model. J Orthop Res 1989;7:709-22.

6. Gresser JD, Hsu S-H, Nagaoka H, Lyons CM, Nieratko DP, Wise DL, Barabino GA and Trantolo DJ. Analysis of a vinyl pyrrolidone/poly(propylene fumarate) resorbable bone cement. J. Biomed. Mater. Res. 1995,;29: 1241–1247.

7. Gresser JD, Trantolo DJ, Nagaoka H, Wise DL, Altobelli DE, Yaszemski MJ, and Wnek GE. Bone cement Part 1: Biopolymer for avulsive maxillofacial repair. In:

Human Biomaterials Applications. Editors. Wise DL, Gresser JD, Trantolo DJ, Yaszemski MJ, Humana Press, Inc., Totowa, New Jersey, 1996; 169–187.

8. Laftman P, Hornstron T, Kairento A, Nilsson OS, Sigurdsson F, Stromberg. No effect of growth hormon on recovery of load-protected bone: Cortical bone mass and strength studied in rabbits. Acta Orthop Scand 1988;59:24-8.

9. Ledet EH, Sachs BL, Brunski JB, Gatto CE, Donzelli PS. Real-time in vivo loading in the lumbar spine: Part 1. Interbody implant: load cell design and preliminry results. Spine 2000; 25:2595-2600.

10. Lewandrowski KU, Cattaneo MV, Gresser JD, Wise DL and Trantolo DJ. Effect of a poly(propylene fumarate) foaming cement on healing of critical size bone defects. Tissue Engineering 1999; 5 (4): 305–316.

11. Lim TH, Goel VK, Winterbottom JM, et al. A comparison of stress-induced porosity due to conventional and a modified spinal fixation device. J Spinal Disord 1994;7:1-11.

12. Lorenz M, Zindrick M, Shwaegler P, et al. A comparison of single-level fusions with and without hardware. Spine 1991;16:S455-8.

13. Liu Q, de Wijn JR, de Groot K, van Blitterswijk CA. Surface modification of nanoapatite by grafting organic polymer. Biomaterials 1998; 19(11-12):1067–72.

14. Kandziora F, Kerschbaumer F, Starker M, Mittlmeier T. Biomechanical assessment of the transoral plate fixation for atlantoaxial instability. Spine 2000;25, 1555-1561.

15. McAfee PC, Farey ID, Sutterlin CE, Gurr KR, Warden KE, Cunningham BW. Device-related osteoporosis with spinal instrumentation. Spine 1989;14:919-26.

16. McAfee PC, Farey ID, Sutterlin CE, Gurr KR, Warden KE, Cunningham BW. The effect of spinal implant rigidity on vertebral bone density: A canine model. Spine 1991;16:S190-97.

17. Nachemson A, Morris JM. In vivo measurements of intradiscal pressure. Discometry, a method for determination of pressure in the lower lumbar discs. J Bone Joint Surg 1994;64-A:1077-1092.

18. Nibu K, Panjabi MM, Oxland T, Cholewicki J. Multidirectional stabilising potential of BAK interbody spinal fusion system for anterior surgery. J Spinal Disord 1997;10:357-362

19. Ohlin A, Karlsson M, Duppe H, Hasserius R, Redlund-Johnell I. Complications after transpedicular stabilization of the spine: A survivorship analysis of 163 cases. Spine 1994;19:2774-9.

20. Rapoff AJ, Ghanayem AJ, Zdeblick TA. Biomechanical comparison of posterior lumbar interbody fusion cages. Spine 1997;22:2375-2379

21. Smith KR, Hunt TR, Asher MA, Anderson HC. The effect of a stiff spinal implant on the bone-mineral content of the lumbar spine in dogs. J Bone Joint Surg [Am] 1991;73:115-23.

22. Schimandle JH, Boden SD. Spine Update: The use of animal models to study spinal fusion. Spine 1994;19:1998-2006.

23. Shirado O, Zdeblick TA, McAfee PC, Cunningham BW, DeGroot H, Warden KE. Quantitative histologic study of the influence of anterior spinal instrumentation and biodegradable polymer on lumbar interbody fusion after corpectomy: A canine model. Spine 1992;17:795-803.

24. van der Elst M, Bramer JAM, Klein CPAT, de Lange ESM, Patka P, Haarman HJTM. Biodegradable interlocking nails for fracture fixation. Clin Orthop 1998;357:192 204.

25. Viijanen J, Kinnunen J, Bondestam S, Majoia A, Rokkanen P, Tormalla P. Bone changes after experimental osteotomies fixed with absorbable self-reinforced poly-L-lactide screws or metallic screws studied by plain radiographs, quantitative computed tomography and magnetic resonance imaging. Biomaterials 1995;16:1353 8.

26. Whitecloud TS, Butler JC, Cohen JL, Candelora PD. Complications of the variable spinal plating system. Spine 1989;14:472-6.

27. Wilke H, Neef P, Hinz B, Seidel H, Cleas L. Intradiscal pressure together with anthropometric data- a data set for validation of models. Clin Biomech 2001;16:111-126.

28. Zdeblick TA, Shirado O, McAfee PC, DeGroot H, Warden KE. Anterior spinal fixation after lumbar corpectomy: a study in dogs. J Bone Joint Surg [Am] 1991;73:527-34.

29. Zdeblick TA. A prospective, randomized study of lumbar fusion: Preliminary results. Spine 1993;18:983-91.

30. Ying JY, Mehnert CP, and Wong MS. Synthesis and applications of supramolecular-templated mesoporous materials. Angew. Chem. Int. Ed. 1999; 38(1): 56–77.

31. Zhang Z, Gekhtman D, Dresselhaus MS and Ying JY. Processing and characterization of single-crystalline ultrafine bismuth nanowires. Chem. Mater.1999; 11(7):1659–1665.

32. Zhang L, Sun T and Ying JY. Oxidation catalysis over functionalized metalloporphyrins fixated within ultralarge-pore transition metal-doped silicate supports. Chem. Commun. 1999; 1103–1104.

FIGURE LEGENDS

Fig. 1: a) The metallic, threaded, hollow, porous titanium BAK cage was obtained from Spine Tech, Inc. (Minneapolis, MN, USA), b-d) BIO-cage 1 to 3 (Cambridge Scientific, Inc. Boston, MA, USA) were manufactured from the same polymer (poly(L-lactide-co-D,L-lactide), Resomer LR 708 (Boehringer-Ingelheim Mannheim, Germany). BIO-cage 1 consisted of pure polymer. BIO-cage 2 consisted of polymer plus 10 micron size (20%w/w) hydroxyapatite buffer. BIO-cage 3 consisted of polymer (75%w/w) plus hydroxyapatite 10 micron size (20%w/w) plus nano-sized hydroxyapatite (5%w/w).

Fig. 2: Scanning electron micrograph of a PPF foaming cement: (A) 5 × showing large pores measuring approximately 0.5 – 3 mm in diameter and (B) 200 × small pores ranging from 50 to 400 μm in diameter.

Fig. 3: Testing setup showing the material testing machine (Zwick 1456, Zwick GmbH, Ulm, Germany). Applied forces were measured with an axial load cell (Z 12, HBM, Darmstadt, Germany) mounted on the testing frame.

Fig. 4 Results of the ROM analysis normalized to the intact L4/5 motion segment.

Fig. 5 Results of the stiffness testing normalized to the intact L4/5 motion segment.

Fig. 6 Results of the axial compression testing normalized to the intact L4/5 motion segment.

Fig. 7 Mode of failure: a) All Bio-cages 1 failed by viscoelastic deformation. b – c) BIO-cages 2 and 3 collapsed and fractured.

FIGURES

Figure 1

Fig. 1: a) The metallic, threaded, hollow, porous titanium BAK cage was obtained from Spine Tech, Inc. (Minneapolis, MN, USA), b-d) BIO-cage 1 to 3 (Cambridge Scientific, Inc. Boston, MA, USA) were manufactured from the same polymer (poly(L-lactide-co-D,L-lactide), Resomer LR 708 (Boehringer-Ingelheim Mannheim, Germany). BIO-cage 1 consisted of pure polymer. BIO-cage 2 consisted of polymer plus 10 micron size (20%w/w) hydroxyapatite buffer. BIO-cage 3 consisted of polymer (75%w/w) plus hydroxyapatite 10 micron size (20%w/w) plus nano-sized hydroxyapatite (5%w/w).

Figure 2

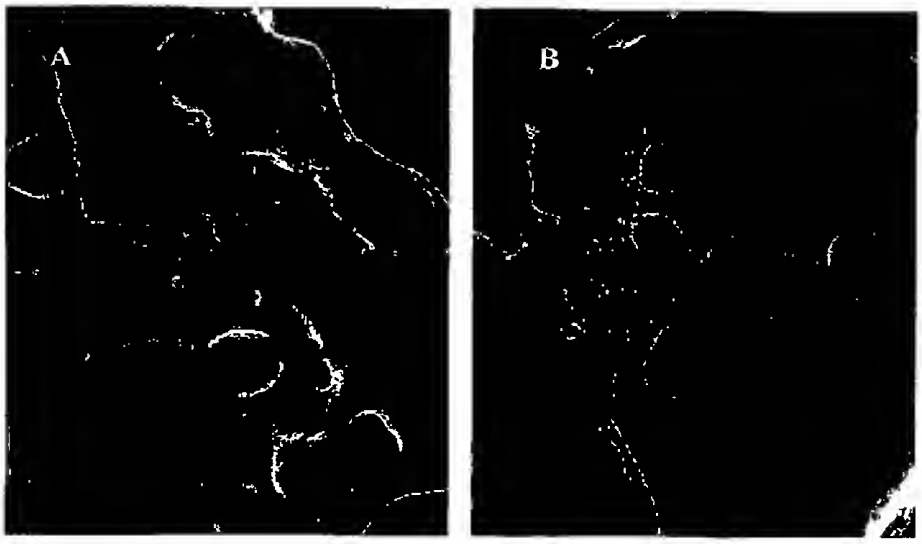

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Figure 3

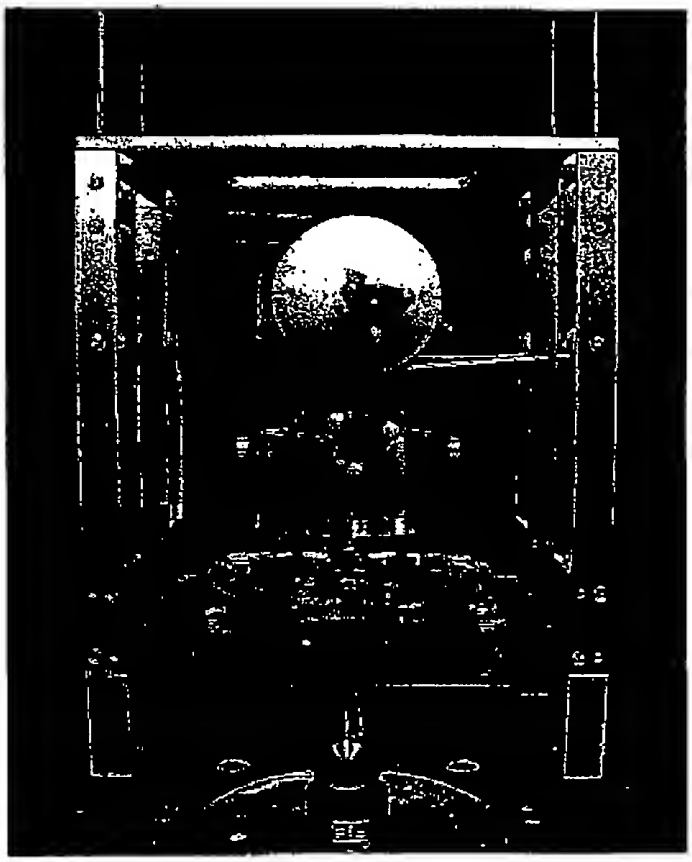

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Figure 4

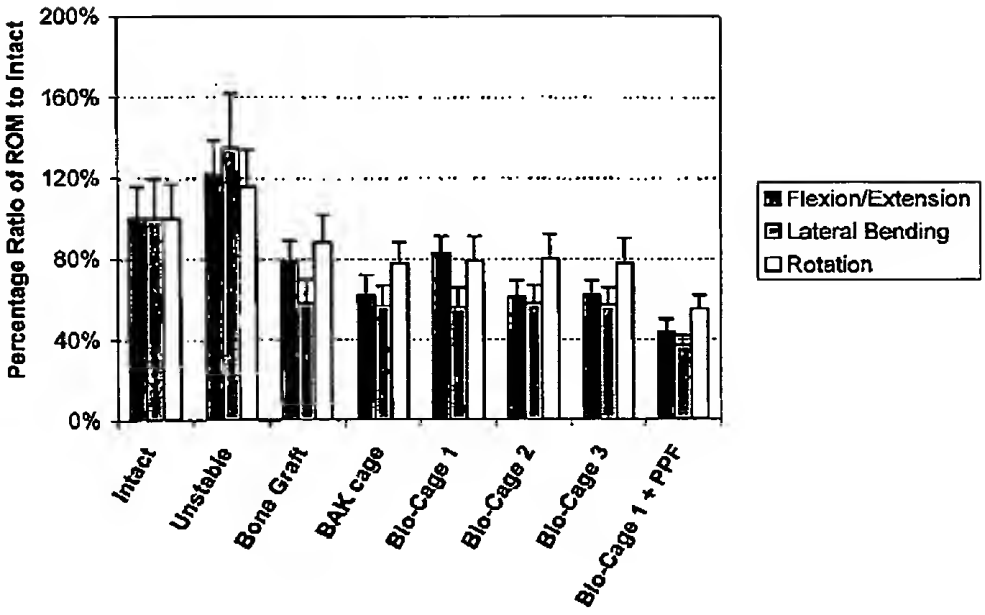


Fig. 4 Results of the ROM analysis normalized to the intact L4/5 motion segment.

Figure 5

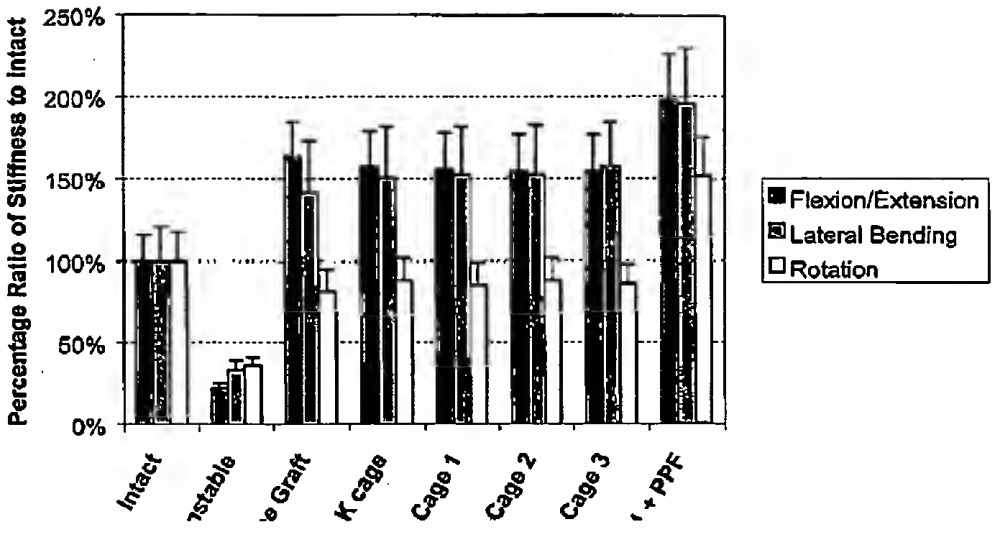


Fig. 5 Results of the stiffness testing normalized to the intact L4/5 motion segment.

Figure 6

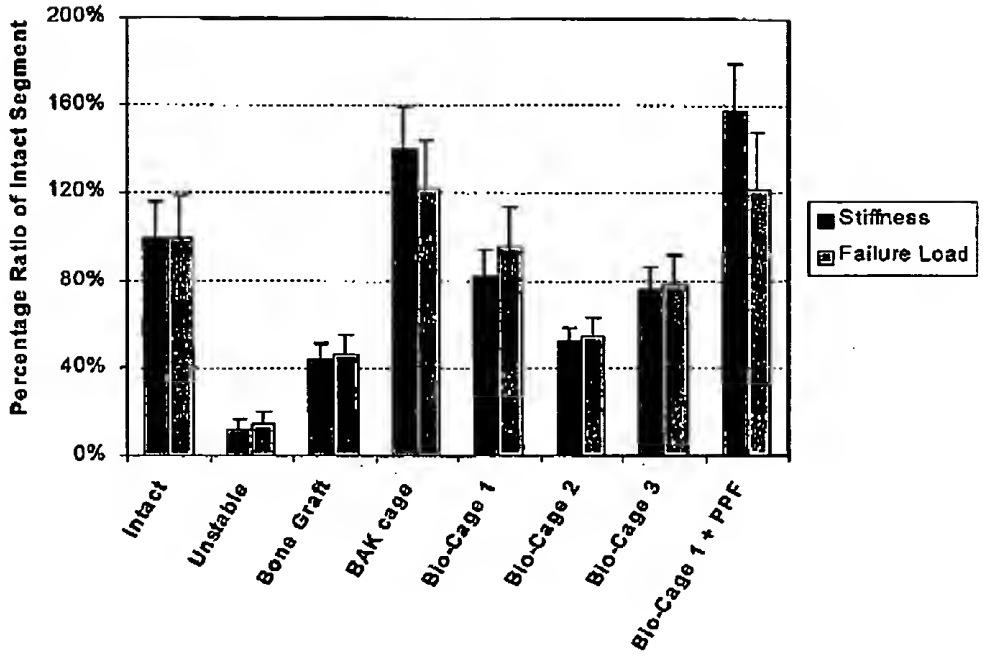
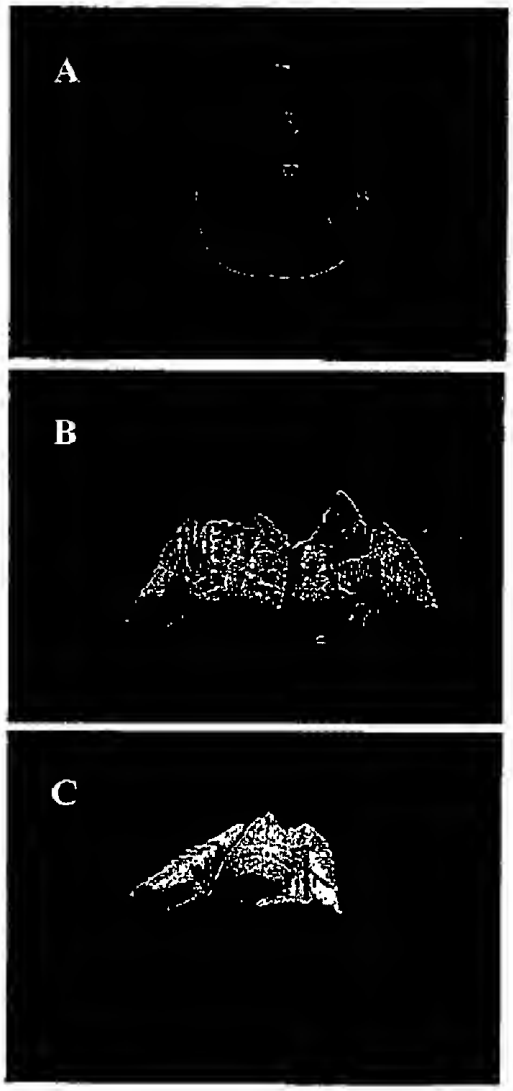


Fig. 6 Results of the axial compression testing normalized to the intact L4/5 motion segment.

Figure 7



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TABLES

Table 1: General Composition of The Two-Part Formulation

Part I (Wt., mg	(Wt. %)	Part II (Wt., mg	(Wt. %))
PPF 1179.5	(47.2)	VP 380.0	(15.2)
HA 341.5	(13.7)	DMPT 0.65	(0.03)
SB 51.3	(2.1)	H2O 450.0	(18.0)
CtA 43.4	(1.7)	Total 845.65	(33.2)
BP 52.5	(2.1)		
Total 1668.2	(66.8)		

PPF: Poly propylene fumarate
HA : Hydroxyapatite
BP: Benzoyl peroxide
SB: sodium bicarbonate
CtA: citric acid
VP: Vinyl pyrollidinone
DMPT: Dimethyl para toulidene
H2O: Distilled water